PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2024,51(8):1834~1847
www.pibb.ac.cn

PD-1/PD-L1轴的作用及其在胃肠道肿瘤免疫治疗中的意义*

曹 馨[1,2] 张进萍[2] 涂丽英[1,2] 邹云莲[2]**
([1] 昆明理工大学医学部，昆明 650500；[2] 云南省第一人民医院血液科，昆明 650100）

摘要 程序性死亡受体1（PD-1）是一种抑制性免疫检查点，与程序性死亡受体配体1（PD-L1）结合，调节免疫反应，维持机体免疫系统平衡。肿瘤细胞通过过表达PD-L1与免疫细胞表面的PD-1结合，抑制免疫细胞的活性与功能，导致癌细胞免疫逃逸和肿瘤进展。胃肠道癌症是全球临床上常见且高死亡率的恶性肿瘤，目前系统治疗方案的效果有限。近年来，免疫检查点抑制剂（immune checkpoint inhibitors，ICIs），如PD-1/PD-L1抑制剂在癌症治疗中越来越重要。免疫疗法已被纳入一些胃肠道恶性肿瘤的治疗方案中，与传统治疗方法不同，它是利用各种手段刺激和增强机体免疫功能，最终达到控制肿瘤细胞的治疗策略。然而，尽管PD-1/PD-L1抑制剂在胃肠道肿瘤治疗中显示出潜力，但单一抑制剂治疗效果有限，这可能是由于肿瘤在抑制剂治疗后仍能通过其他途径逃逸免疫攻击，或者存在其他免疫抑制因子的调节。因此，为了进一步提高治疗效果，组合疗法日益受到重视，它可以同时作用于不同的免疫途径，提高免疫治疗的综合效果。然而，为了实现有效的组合疗法，需要深入研究PD-1/PD-L1轴在胃肠道肿瘤发生和发展中的具体作用机制，这有助于制定最佳的治疗策略，并为合适的患者群体提供个体化的治疗方案。本文将介绍PD-1/PD-L1轴在肿瘤发生中的作用及其机制研究进展，并综述PD-1和PD-L1抑制剂在胃肠道肿瘤中的单一和联合治疗策略。

关键词 程序性死亡受体1，程序性死亡受体配体1，胃肠道肿瘤，免疫治疗
中图分类号 Q2，R3 **DOI**：10.16476/j.pibb.2023.0434

在肿瘤微环境（tumor microenvironment，TME）中，程序性死亡受体配体1（PD-L1）在肿瘤细胞表面表达，与T细胞上的程序性死亡受体1（PD-1）结合，抵抗T细胞的杀伤作用，最终引起肿瘤细胞免疫逃逸。应用PD-1/PD-L1抑制剂阻断PD-1/PD-L1信号通路，在多种实体瘤中显示出优异的抗肿瘤疗效[1]。然而，临床研究表明，一些患者对治疗没有反应或者在缓解一段时间后表现出肿瘤复发[2]。因此，深入了解PD-1/PD-L1轴的调控对于改善抗肿瘤免疫治疗至关重要。

PD-1/PD-L1检查点抑制剂旨在阻断由肿瘤细胞表达的PD-L1与由肿瘤浸润性T细胞表达的PD-1之间的相互作用，恢复抗肿瘤T细胞反应和促进肿瘤消退。有研究显示，PD-L1在肿瘤上的高表达与胃肠道癌的晚期疾病状态和不良预后密切相关[3-4]。目前，针对PD-1/PD-L1信号通路的免疫疗法已成为某些癌症的一线治疗方法，因为它们能在特定的晚期癌症患者中促进持久的抗肿瘤免疫反应，因此已有8种靶向PD-1/PD-L1的抗体抑制剂获得美国食品和药物管理局（FDA）批准，包括5种抗PD-1抗体（Nivolumab、Pembrolizumab、Cemiplimab、Dostarlimab和Retifanlimab）和3种抗PD-L1抗体（Avelumab、Atezolizumab和Durvalumab）。尽管PD-1/PD-L1靶向疗法对多种癌症具有临床益处，但接受PD-1/PD-L1抑制剂作为单一治疗的患者表现出低客观反应率和获得性肿瘤耐药[5]。因此，需要通过将PD-1/PD-L1靶向治疗与其他免疫疗法、化学疗法、放射疗法或其他方式相结合来提高患者的反应率。

1 PD-1/PD-L1结构及功能

PD-1（CD279）是一种免疫抑制受体，属于

* 云南省科技厅科技计划（202101AY070001-027）和云南省临床医学中心开放项目（2020LCZXKF-XY08）资助。
** 通讯联系人。
Tel：13708893386，E-mail：zouyunlian825046@sina.com
收稿日期：2023-11-06，接受日期：2024-03-04

CD28家族，由位于染色体2q37.3的*PDCD1*基因编码[6]，主要表达于活化的T细胞、B细胞、间充质干细胞、自然杀伤细胞、单核细胞和部分肿瘤细胞[7]。PD-1是含有单个细胞外IgV结构域、疏水性跨膜结构域和细胞质尾部结构域的I型跨膜糖蛋白（表1）。细胞质尾部包含2个酪氨酸基序、1个基于免疫受体酪氨酸的抑制基序（immunoreceptor tyrosine-based inhibitory motif，ITIM）和1个基于免疫受体抑制酪氨酸的开关基序（immunoreceptor tyrosine-based switch motif，ITSM），当PD-1与PD-L1结合时，ITIM就会被磷酸化，并通过与下游信号通路分子结合，抑制T细胞的免疫应答[8]。

PD-L1（CD274，B7-H1）是PD-1的配体，由位于染色体9p24.1的*CD274*基因编码，主要表达在抗原呈递细胞（antigen presenting cells，APC）和实质组织细胞以及癌细胞表面大量表达[9-12]。PD-L1是含有IgV和IgC结构域、疏水跨膜结构域和细胞质尾部结构域的I型糖蛋白（表1）。PD-1和PD-L1之间的相互作用导致ITSM结构域的PD-1细胞质区域酪氨酸残基的磷酸化，募集含有Src同源2结构域的蛋白质酪氨酸磷酸酶2（SHP-2），反过来导致下游蛋白酪氨酸激酶（Syk）和磷脂肌醇3激酶（PI3K）被磷酸化，从而抑制下游信号转导和T细胞生物学功能，包括淋巴细胞增殖、细胞因子分泌和细胞毒性T淋巴细胞（cytotoxic T lymphocytes，CTL）细胞毒性。这种相互作用导致肿瘤特异性T细胞凋亡和耗竭，使肿瘤细胞能够逃避T细胞的免疫监视。

PD-1/PD-L1通路在自身免疫性疾病、病毒感染、移植免疫学和肿瘤免疫中发挥重要作用[13-16]。在正常情况下，PD-1/PD-L1通路对维持外周免疫耐受，预防过度组织炎症和自身免疫性疾病有积极作用。然而，随着肿瘤的发生和发展，肿瘤微环境中的PD-L1在肿瘤细胞和APC上异常高表达，PD-1/PD-L1信号转导的激活可引起PD-1细胞质ITIM和ITSM结构域中酪氨酸残基的磷酸化，通过诱导细胞凋亡、抑制颗粒酶和穿孔素的产生、降低γ干扰素（IFN-γ）、白介素-2（IL-2）和肿瘤坏死因子α（TNF-α）分泌以及停滞细胞周期来降低肿瘤浸润淋巴细胞（tumor-infiltrating lymphocyte，TILs）的抗肿瘤活性[8，17]。

Table 1　Structure of PD−1 and PD−L1

表1　PD−1和PD−L1的结构

分子	基因名称	配体	表达模式	基因结构	蛋白质结构
PD-1	*PDCD1*	PD-L1和PD-L2	a. 活化的T细胞、B细胞、间充质干细胞、自然杀伤细胞和单核细胞 b. 部分癌细胞	人类染色体2号的2q37.3区域，由五个外显子组成	a. 细胞外包含单个IgV结构域 b. 细胞质尾巴含有ITIM和ITSM
PD-L1	*CD274*	PD-1和CD80	a. APC b. 实质组织细胞 c. 部分癌细胞	人类染色体9号的p24.1区域，由四个外显子组成	a. 细胞外包含IgV和IgC结构域 b. 跨膜结构域 c. 细胞质尾部

2　PD−1/PD−L1表达的调控机制

2.1　PD−1的调节机制

在*PDCD1*的转录和翻译过程中，位于*PDCD1*基因转录起始位点（transcription start site，TSS）上游的CR-B和CR-C两个保守区域起着重要作用[18]。研究人员发现，PD-1表达的转录调控和表观遗传调控中都存在与这两个保守区域密切相关的调节因子。在转录调控方面，CR-B区包含激活蛋白1（activator protein-1，AP-1）和负调节转录因子T-bet的结合位点。AP-1是由4个亚家族（Fos、Jun、ATF和Maf）组成的一类转录因子，它通过调节相关靶基因的表达参与细胞增殖、分化和凋亡过程[19]。在肿瘤浸润T细胞上发现，大量AP-1亚基Fos与JunB蛋白复合物，与CR-B区的AP-1结合位点结合，上调PD-1的表达[20]。T-bet是具有抑制PD-1转录能力的调节因子，经T细胞抗原受体（T cell antigen receptor，TCR）信号刺激后，它可以通过直接结合CR-B区域的相应位点来负调节PD-1转录，下调PD-1的表达[21]。与CR-B区相比，CR-C区具有更丰富的调控位点，包括活化T细胞核因子（NFATc1）、核因子κB（NF-κB）、IFN刺激反应元件（ISRE）和叉头转录因子1（FoxO1）结合位点[22]。在CD8+T细胞中，转录因子NFATc1在TCR信号刺激下与CR-C区域内的对应元件结合以启动PD-1转录，促进PD-1表达[18]。

在巨噬细胞活化过程中，NF-κB的p65亚基与CR-C区的NF-κB位点结合，激活*PDCD1*转录后，促进PD-1表达[23]。在CD8 T细胞和巨噬细胞中，当IFN-α激活JAK/STATs信号通路时，干扰素反应因子9（IRF9）和STAT1-STAT2异二聚体结合形成IFN刺激的基因因子3（ISGF3），然后与ISRE结合，促进PD-1表达[24]（图1）。基因启动子区域的DNA甲基化会抑制基因转录[25]，CR-B和CR-C在不表达PD-1的幼稚T细胞中完全甲基化，但在幼稚T细胞感染病毒分化为效应CD8+T细胞的过程中，PD-1表达水平持续上调，这两个区域的甲基化水平逐渐降低，两者之间呈显著负相关[26]，这表明CR-B和CR-C区域的甲基化程度对PD-1表达具有重要的调控作用（表2）。

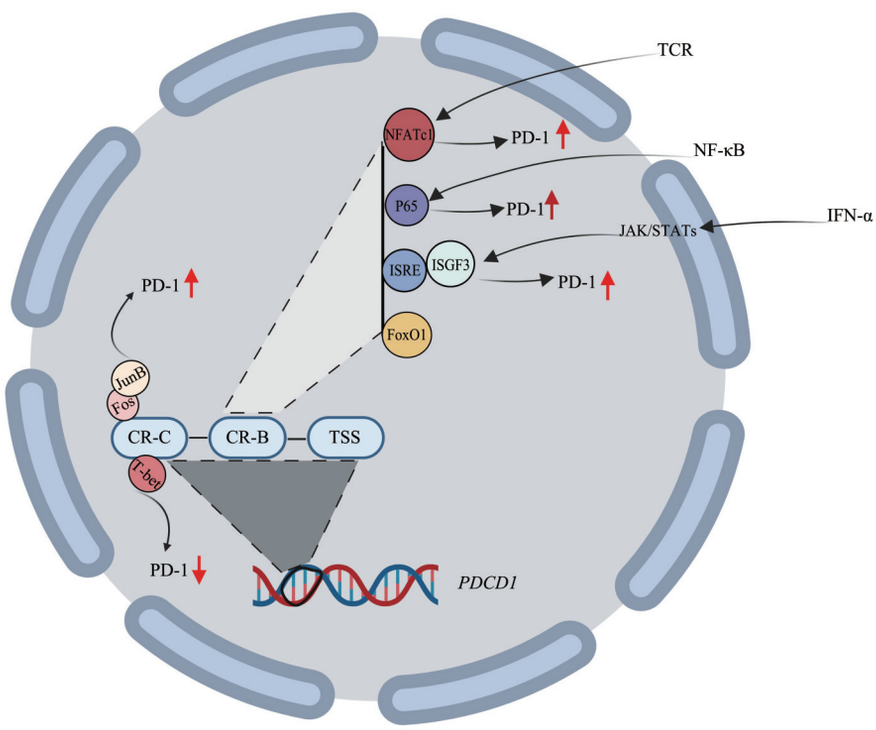


Fig. 1 Transcriptional regulation of PD−1 expression

图1 PD−1在转录水平上的表达

NFATc1：活化T细胞核因子；NF-κB：核因子κB；ISRE：IFN刺激反应元件；FoxO1：叉头转录因子1结合位点；ISGF3：IFN刺激的基因因子3；TCR：T细胞抗原受体；IFN-α：α干扰素（Biorender网站绘制）。

Table 2 Regulation mechanisms of PD−1

表2 PD−1的调控机制

调控类型	细胞信号调控网络	关键过程	影响	参考文献
转录调控	TCR/钙调磷酸酶/NFATc1信号通路	NFATc1的激活	阳性	[27]
	T-bet、Blimp-1	与*PDCD1*基因的相应部分结合	阴性	[28-29]
	STAT3（IL-6）和STAT4（IL-12）、AP-1	与*PDCD1*基因的相应部分结合	阳性	[30]
	NF-κB信号通路	NF-κB的表达增加	阳性	[31]
	JAK/STATs信号通路	干扰素刺激基因因子3（ISGF3）的形成	阳性	[32]
	Notch信号通路	重组信号结合蛋白免疫球蛋白κJ区（RBPJk）和Notch1胞内结构域（NICD）的形成	阳性	[33]
转录后调控	miR-138、miR-28	作用于PD-1 mRNA的3'-UTR	阴性	[34]
翻译后修饰	FBXO38型	促进PD-1蛋白的泛素化	阴性	[35]
	CR-B和CR-C	甲基化水平较低	阳性	[26]
表观遗传调控	富含AT的特殊序列结合蛋白1（SATB-1）	募集核小体重塑脱乙酰酶（NURD）复合物	阴性	[36]
	核小体蛋白（CBX4）	CR-B和CR-C位点积累抑制性组蛋白	阴性	[37]

2.2　PD-L1的调节机制

PD-L1在肿瘤细胞中的表达不仅受促癌信号通路和TME的调控，还受多种细胞因子外源性诱导，包括IFN-γ、TNF-α、白介素（ILs）和表皮生长因子（EGF）等多种细胞因子，它们通过JAK/STAT1/IRF1、NF-κB、PI3K/AKT/mTOR和JAK/STAT3信号通路外源诱导PD-L1表达[38-39]（表3）。在三阴性乳腺癌（TNBC）中，泛素连接酶E3组分N识别蛋白5（UBR5），通过上调蛋白激酶RNA（PKR）激活PKR的下游因子来增强*CD274*的反式活化，上调PD-L1的表达[40]。PD-L1的调控还与肿瘤内基因突变和扩增有关，在原发性纵隔大B细胞淋巴瘤、小细胞肺癌、鳞状细胞癌和EBV阳性胃癌中，当位于染色体9p24.1的拷贝数增加，引起*CD274*扩增，PD-L1表达水平增加[41-43]。

Table 3　Regulation Mechanisms of PD-L1

表3　PD-L1的调控机制

调控类型	细胞信号调控网络	关键过程	影响	参考文献
转录调控	NF-κB信号通路	NF-κB的表达增加	阳性	［44］
	HIF-1α信号通路	HIF-1α的表达增加	阴性	［45］
	IFN-γ信号通路	IRF-1和IRF-2的激活	阳性	［46］
	PI3K/AkT信号通路	PTEN缺失导致PI3K的激活	阳性	［47］
	EGFR/ERK1/2/c-Jun信号通路	c-Jun的激活	阳性	［48］
	Hippo信号通路	RNF31与YAP蛋白结合	阴性	［49］
	MYC	MYC直接与*PD-L1*启动子结合	阳性	［50］
	转录因子AP-2家族的亚型α（AP-2α）	AP-2α直接与*PD-L1*启动子结合	阴性	［51］
转录后调控	miR-155、miR-181b和miR-186	作用于PD-L1 mRNA的3'-UTR	阴性	［52］
	miR-183-5p	抑制PTEN表达	阳性	［53］
翻译后修饰	含有重复β转导素蛋白质（β-TrCP）	促进PD-L1蛋白的泛素化	阴性	［54］
	CMTM6/CMTM4	抑制PD-L1蛋白的泛素化	阳性	［55］
	CSN5	促进PD-L1蛋白的去泛素化	阳性	［56］
	GSK3β	促进PD-L1蛋白的磷酸化	阴性	［57］
	IL-6/JAK1通路	促进PD-L1蛋白的糖基化	阳性	［58］
	B3GNT3	促进PD-L1蛋白的糖基化	阳性	［59］
	ATXN3	促进PD-L1蛋白的去泛素化	阳性	［60］
表观遗传调控	MLL1-H3K4me3轴	组蛋白甲基化	阳性	［61］
	CD274启动子中一些CpG位点的甲基化	DNA甲基化	阴性	［62］
	组蛋白脱乙酰酶（HDAC）	组蛋白乙酰化	阴性	［63］

3　PD-1/PD-L1表达促进肿瘤发生的机制

3.1　PD-1/PD-L1表达抑制抗癌免疫促进肿瘤发生

PD-1/PD-L1信号轴调节免疫反应以防止免疫细胞的过度激活和自身免疫疾病的发生[64]。肿瘤细胞表达的PD-L1与TILs表面的PD-1结合，阻断TILs活化，导致细胞因子减少，包括肿瘤坏死因子、IFN-γ和IL-2[65]，进而促进免疫逃逸和肿瘤进展，最终在肿瘤中诱导免疫抑制微环境。PD-1/PD-L1抑制剂靶向共抑制途径，可以激活机体自身的抗肿瘤免疫反应，有效抑制肿瘤生长甚至治愈肿瘤[66]。然而，与分子靶向治疗和化疗相比，免疫疗法具有较高的耐药性，这是临床中不可忽视的问题，在胃癌小鼠模型中，PD-1抑制剂与化疗药物的联合使用可以减少髓源性抑制细胞（myeloid-derived suppressor cells，MDSCs）的数量，以增加PD-1抑制剂的作用，从而促进CD8+T细胞对肿瘤的浸润，说明MDSC有助于抗PD-1耐药性。然而，使用化疗药物会诱导肿瘤细胞表达PD-L1，PD-L1会促进肿瘤发生和MDSC的积累[67]，因此将PD-1阻断与MDSC靶向相结合可能成功克服对免疫检查点阻断疗法（ICB）的耐药性。PD-1/PD-L1耐药性已被证明与PD-1/PD-L1表达水平、第一或共刺激信号受损、肿瘤免疫微环境有关。

3.2　PD-1内源信号参与肿瘤的发生

在默克尔细胞癌（MCC）中，肿瘤细胞内源性PD-1通过激活下游mTOR-线粒体活性氧类

（reactive oxygen species，ROS）信号转导促进肿瘤生长，而与适应性免疫无关[68]。因此，联合抑制PD-1和mTOR或线粒体ROS可能是MCC的潜在治疗策略。肿瘤细胞内源性PD-1表达也见于其他几种恶性肿瘤，包括黑色素瘤[69]、肝细胞瘤（HCC）[70]、胶质母细胞瘤[71]、胰腺癌（PC）[72]、非小细胞肺癌（NSCLC）[73]和结直肠癌（CRC）[74]。与在MCC中的发现类似，前三种肿瘤细胞通过表达PD-1激活mTOR，促进肿瘤的发生，与此一致的是，PC的肿瘤细胞通过表达PD-1激活Hippo信号通路，也促进肿瘤的发生。后两种癌症的肿瘤细胞通过表达PD-1抑制PI3K/AKT或MAPK信号通路，抑制肿瘤的发生。这些证据表明，肿瘤细胞内源性PD-1在各种肿瘤中起着不同的作用，因此抗PD-1药物在不同肿瘤中有不同的治疗效果。

3.3 PD−L1内源信号参与肿瘤发生发展

PD-L1在肿瘤中的内在信号，通过促进癌症干性、细胞增殖和侵袭、上皮-间充质转化（epithelial-mesenchymal transition，EMT）和化疗耐药性来促进肿瘤进展。新出现的肿瘤可能受益于PD-L1的表达，以克服癌症发生的一个或多个障碍。后期，肿瘤衍生的PD-L1可能会进一步限制抗肿瘤免疫并促进肿瘤发生。

在HCC中，PD-L1激活了SGK2/β-catenin信号通路，以诱导EMT和获得癌症干细胞（CSC）表型[75]。类似的是，在NSCLC中，PD-L1通过激活Wnt/β-catenin信号转导发挥致癌功能[76]。在口腔鳞状细胞癌（OSCC）中，PD-L1通过Jak2-Stat3/MAPK-AP1信号通路，支持OSCC的存活、侵袭和治疗耐药性[77]。最近的一项研究表明，肿瘤PD-L1可以通过稳定EMT转录因子Snail来驱动TNBC的EMT[78]。这些研究揭示了PD-L1在多种癌症类型中的复杂作用，以及PD-L1介导的信号通路的重要性。进一步的研究有助于更好地理解这些信号通路的调控机制，并为相关癌症的治疗提供新的治疗策略和靶点。

4 PD−1/PD−L1抑制剂在胃肠道肿瘤免疫治疗中的应用

2020年全球约有1 930万新发癌症病例和近1 000万癌症死亡病例，胃肠道癌症占新发病例的19.8%，占新发死亡病例的29.6%[79]。胃肠道癌是主要恶性疾病，包括胃癌和结直肠癌。迄今为止，现代手术切除和放化疗（radiation therapy and chemotherapy，CRT）结合仍然是胃肠癌患者的主要治疗方案，但由于癌症进展迅速以及CRT耐药，晚期胃肠道癌症患者的总体5年生存率低于15%[80]。为了改善胃肠道癌症的预后，免疫靶向治疗已成为癌症治疗的最佳选择，多项PD-1/PD-L1抑制剂的临床实验正在进行（表4）。

Table 4 Clinical studies of PD−1/PD−L1 inhibitors in gastrointestinal tumors

表4 PD−1/PD−L1抑制剂在胃肠道肿瘤的临床研究

免疫检查点抑制剂	联合治疗	肿瘤类型	阶段	NCT编号
Pembrolizumab	顺铂+5-氟尿嘧啶＋卡培他滨	晚期胃癌或胃食管交界处腺癌	3	NCT02494583
Pembrolizumab	贝伐珠单抗＋比尼美替尼	难治性结直肠癌	2	NCT03475004
Nivolumab	卡博替尼	转移性难治性结直肠癌	2	NCT04963283
Nivolumab	伊匹木单抗	早期缺失错配修复缺陷直肠癌患者	2	NCT05732389
Atezolizumab	考比替尼＋瑞戈非尼	局部晚期或转移性结直肠癌	3	NCT02788279
Atezolizumab	贝伐珠单抗＋卡培他滨	难治性转移性结直肠癌	2	NCT02873195
Durvalumab	曲美木单抗	晚期结直肠癌	2	NCT02870920
Nivolumab	Andecaliximab	不可切除或复发的胃癌或胃食管交界处腺癌	2	NCT02864381
Pembrolizumab	卡培他滨＋曲妥珠单抗	晚期胃癌或胃食管交界处腺癌	2	NCT04249739
Durvalumab	曲美木单抗＋卡博替尼	胃食管癌和其他胃肠道恶性肿瘤	2	NCT03539822
Pembrolizumab	立体定向放疗	肝转移性结直肠癌	1	NCT02837263
Retifanlimab	玛格妥昔单抗＋5-氟尿嘧啶＋奥沙利铂	胃癌	3	NCT04082364
Tebotelimab	玛格妥昔单抗＋5-氟尿嘧啶＋奥沙利铂	胃癌	3	NCT04082364
Cemiplimab	菲安利单抗	局限性或局部晚期的微卫星不稳定型结直肠癌	2	NCT06205836

4.1　胃癌（gastric cancer，GC）

尽管过去几十年全球胃癌发病率稳步下降，但GC仍然是全球最关注的癌症之一。截至2020年，GC的发病率在全球排名第五，死亡率在全球排名第四[79]。GC具有高度异质性、缺乏特定症状，患者早期不易发现，往往病情恶化才得以发现[81-82]。目前GC患者的首选治疗方案是手术切除联合辅助放化疗[83]。然而，晚期GC患者的高复发率导致大量患者死亡[84]。常规疗法的临床疗效有限，免疫治疗作为肿瘤治疗突破口已成为继手术、化疗、放疗和靶向治疗之后的有效治疗方式[85]。ICIs的重大进展已经开始改变胃癌临床治疗。

GC的联合治疗因快速发展的ICIs领域而得到丰富。基于临床II期和III期试验[86-91]，PD-1抑制剂Nivolumab和Pembrolizumab已在欧洲、美国的一线或三线临床中获批用于晚期GC的单药和联合治疗。针对肿瘤细胞和免疫细胞上不同分子靶标的ICIs正在增加，目前与GC有关的几项ICIs药物临床试验：抗PD-1抗体Sintilimab[92]、Tislelizumab[93]、Retifanlimab[94]和Tebotelimab[95]，以及抗PD-L1抗体Atezolizumab[96]、Avelumab[97-98]、Durvalumab[99]（表4）。临床结果显示，ICIs联合化疗的治疗方案优于使用单一抑制剂或仅化疗的效果，即使在含有ICIs的三线治疗方案中发生了更多的毒性，但总体安全性可控，鼓励在以后的治疗中联合使用免疫疗法。

值得注意的是，在15%~20%的GC患者中发现人表皮生长因子受体2（HER2）过表达，对此已经确立的治疗方法是对HER2阳性患者进行HER2阻断[100]，曲妥珠单抗（Trastuzumab）是第一个针对HER2受体的单克隆抗体，与化疗联合作为晚期HER2阳性GC患者的一线治疗[101]。在ICIs的新时代，HER2和PD-1/PD-L1定向疗法的联合疗法产生协同效应，一项临床试验（NCT03615326）将PD-1抑制剂Pembrolizumab联合Trastuzumab和化疗治疗HER2阳性晚期GC患者，试验结果显示，与单独使用Trastuzumab和化疗的疗法相比，将Pembrolizumab添加到Trastuzumab和化疗中使患者客观缓解率（objective respone rate，ORR）显著增加，反应持久且安全可控[102]。

4.2　结直肠癌（colorectal cancer，CRC）

CRC是全球第三大常见的恶性肿瘤，每年新增确诊病例约185万例，死亡病例约85万例[103]，预计到2030年，全球CRC负担将增加60%，新发病例超过220万，死亡人数将超过110万[104]。在新确诊的CRC患者中，20%的患者在诊断时出现转移性疾病，另外25%的患者会在病程中的某个时间点发生转移性疾病[103]。转移性CRC（mCRC）通常采用手术、全身疗法（化疗、免疫疗法、生物疗法）和局部疗法（肝动脉输液泵）进行治疗[105]，根据疾病的进展，这些治疗方式可以联合使用。尽管全身疗法和局部疗法的治疗取得了进展，但mCRC患者的预后仍然很差，1年、3年和5年生存率分别约为70%~75%、30%~35%和20%[103]。

根据CRC错配修复状态分为两类：*MMR*基因缺陷（dMMR）癌细胞的突变率是正常细胞的100~1 000倍[106]，这类肿瘤中微卫星（MSI）不稳定，突变率高，因此这类肿瘤被称为dMMR-MSI-H[107]。与之相对，*MMR*基因良好（pMMR）癌细胞的突变率要低得多，每212个DNA碱基的突变率低于16.48个[108-109]，由于这类肿瘤中的微卫星突变较少，因此这类肿瘤被称为pMMR-MSI-L。

所有CRC患者中约15%是dMMR-MSI-H，这是一个独特的生物标志物定义的人群，值得注意的是，该百分比与肿瘤分期相关，随阶段降低[110]，CRC患者2期、3期、4期肿瘤为dMMR-MSI-H的比例大约为5%~20%、11%、5%[111]。此外，dMMR-MSI-H是不同阶段患者的预后生物标志物[112]，在第2期和第3期，dMMR-MSI-H肿瘤患者的预后远好于pMMR-MSI-L肿瘤患者，值得注意的是，dMMR-MSI-H的4期患者预后不佳，但对免疫检查点阻断反应良好[113]。

因此，研究开发更有效的策略来治疗各种CRC患者的需求格外迫切[114]。在过去的十年中，免疫疗法因其在实体瘤中取得显著而持久的反应而引起了各界极高的关注。目前的研究表明，高肿瘤突变负荷已成为多种肿瘤类型对免疫疗法具有反应性的标志[115-116]，免疫疗法可有效控制肿瘤进展[117]。一些CRC肿瘤具有高突变负荷，可以选择免疫疗法进行治疗。

4.2.1　PD-1抑制剂的单一疗法

目前对免疫疗法疗效的研究，特别是ICB在dMMR-MSI-H CRC患者中的疗效，已呈现出可喜的结果，然而，对于pMMR-MSI-L CRC患者使用抗PD-1抑制剂的免疫疗法并未达到预期效果[118-119]。这些发现使得FDA批准ICIs靶向CTLA4（Ipilimumab）、PD-1（Pembrolizumab和

Nivolumab）和PD-L1（Atezolizumab和Durvalumab）用于治疗dMMR-MSI-H型CRC。且目前在美国，Pembrolizumab和Nivolumab，以及Nivolumab和Ipilimumab的组合，被批准用于CRC。基于III期KEYNOTE-177研究（NCT02563002），Pembrolizumab目前被批准用于dMMR-MSI-H转移性CRC的一线治疗[120]。值得注意的是，B2M和Janus激酶1和2（JAK1/2）突变经常存在于具有微卫星不稳定性的CRC中，普遍认为对CRC患者应用ICB疗法，可能会导致耐药性，但最近的一项研究表明这类患者不应被排除在抗PD-1治疗之外[121]。

NCT01876511临床试验2期数据报道Pembrolizumab对于dMMR-MSI-H CRC，免疫相关客观缓解率和免疫相关无进展生存率分别为40%（10名患者中的4名）和78%（9名患者中的7名）；对pMMR-MSI-L CRC，免疫相关客观缓解率和免疫相关无进展生存率分别为0%和11%（18名患者中的2名）。在dMMR-MSI-H CRC队列中未达到中位无进展生存期和总生存期，但在pMMR-MSI-L CRC队列中分别为2.2个月和5.0个月（疾病进展或死亡的风险比为0.10（*P*<0.001），死亡风险比为0.22（*P*=0.05））。全外显子组测序显示，在dMMR的肿瘤中，每个肿瘤平均有1 782个体细胞突变，而在pMMR的肿瘤中为73个（*P*=0.007），体细胞高突变负荷与无进展生存期延长相关（*P*=0.02）[122]。该试验数据说明，dMMR-MSI-H CRC肿瘤比pMMR-MSI-L CRC肿瘤对PD-1抑制剂Pembrolizumab更敏感。

NCT02060188临床试验2期数据报道，74名CRC患者（dMMR/MSI-H）在至少接受过一次全身治疗后接受了Nivolumab治疗，大多数（54.1%）既往接受过≥3种治疗。在中位随访12个月时，74名患者中有23名（31.1%（95% *CI* 20.8%~42.9%））达到研究者评估的客观反应；68.9%（95% *CI* 57.1%~79.2%）的患者疾病控制时间≥12周。尚未达到中位反应持续时间，所有反应者都活着，8人（34.8%）的反应时间≥12个月。CheckMate 142的结果表明，Nivolumab单一疗法具有良好的耐受性，提供了持久的反应和疾病控制，所有反应者在分析时都活着，并且在dMMR-MSI-H mCRC预先治疗的患者群体中长期存活[123]。

4.2.2 PD-1或PD-L1抑制剂组合其他药物的联合疗法

根据CheckMate-142的Nivolumab加Ipilimumab组合的疗效和安全性结果报告，在119名患者中，76%的患者既往接受过≥2次全身治疗，中位随访13.4个月时，研究者评估的*ORR*为55%（95% *CI*，45.2~63.8），≥12周的疾病控制率为80%。未达到中位反应持续时间，大多数随访（94%）在数据截止时仍在进行中。9个月和12个月的无进展生存率为76%和71%，总生存率为87%和85%。在患者报告的结果中观察到具有统计学意义和临床意义的改善，包括功能、症状和生活质量。32%的患者发生了3~4级治疗相关不良事件，并且这些事件是可控的。Nivolumab加Ipilimumab表现出高反应率、长无进展生存期和可管理的安全性，更关键的是患者报告结果有显著改善。间接比较表明，联合疗法相对于抗PD-1抑制剂单一疗法具有更高的疗效和良好的收益风险特征[124]。

4.2.3 PD-L1抑制剂与抗血管生成抗体联合疗法

PD-L1抑制剂Atezolizumab和抗血管内皮生成因子单抗Bevacizumab的组合在Ib期研究中对10名dMMR/MSI-H MCRC患者进行了测试。该组合具有良好的耐受性，90%的患者达到疾病控制，ORR为30%[125]。

4.2.4 双特异性抗体的免疫疗法

双特异性抗体是一类新兴的靶向治疗药物，旨在结合一个或两个抗原上的两个不同位点。通过靶向两种不同的抗原，同时桥接肿瘤细胞和T细胞，从而增强肿瘤间T细胞的浸润和活化。一种CD137-PD-L1（FS222），在临床前试验中显示出强大的T细胞介导的CRC抗肿瘤活性[126]。

5 结论与展望

PD-1/PD-L1检查点阻断处于研究的最前沿，为癌症患者带来了新治疗方案的希望，这些方案有可能产生实质性的临床益处并延长生存期。PD-1/PD-L1靶向疗法可重新激活免疫系统以诱导免疫介导的肿瘤根除，它们已证明单药成功，在临床上也显示出与常规和靶向疗法的联合使用（图2）。但是PD-1/PD-L1抑制剂在胃肠道肿瘤中的使用有限

（表4），且大部分患者对PD-1/PD-L1靶向治疗无反应或耐药，进一步阐明PD-1及其配体PD-L1在胃肠道癌中的作用将有助于了解免疫治疗的基础，并可能允许识别新的治疗靶点和生物标志物以提高临床疗效。

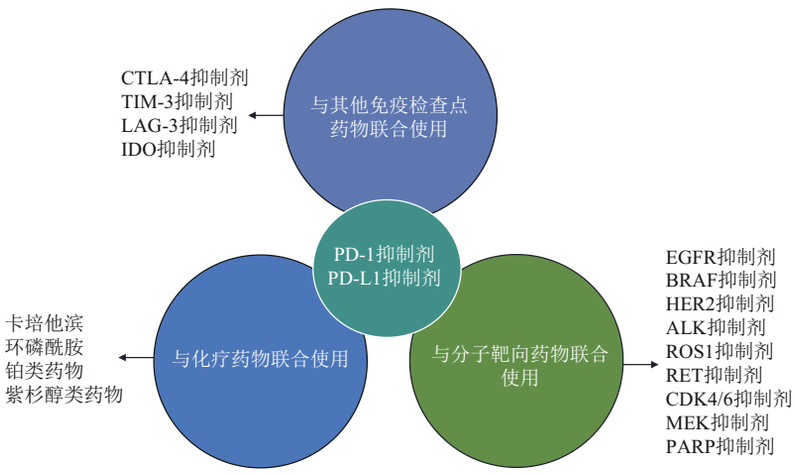


Fig. 2　The various applications of PD1/PD−L1 inhibitors in oncology

图2　PD1/PD−L1抑制剂在肿瘤学中的各种用途

参　考　文　献

[1] Ai L, Xu A, Xu J. Roles of PD-1/PD-L1 pathway: signaling, cancer, and beyond. Adv Exp Med Bio, 2020, **1248**: 33-59

[2] Li W, Wu F, Zhao S, *et al*. Correlation between PD-1/PD-L1 expression and polarization in tumor-associated macrophages: a key player in tumor immunotherapy. Cytokine Growth Factor Rev, 2022, **67**: 49-57

[3] Högner A, Moehler M. Immunotherapy in gastric cancer. Curr Oncol, 2022, **29**(3): 1559-1574

[4] Li Y, Du Y, Xue C, *et al*. Efficacy and safety of anti-PD-1/PD-L1 therapy in the treatment of advanced colorectal cancer: a meta-analysis. BMC Gastroenterol, 2022, **22**(1): 431

[5] Denis M, Grasselly C, Choffour P A, *et al*. *In vivo* syngeneic tumor models with acquired resistance to anti-PD-1/PD-L1 therapies. Cancer Immunol Res, 2022, **10**(8): 1013-1027

[6] Keir M E, Butte M J, Freeman G J, *et al*. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol, 2008, **26**: 677-704

[7] Böger C, Behrens H M, Mathiak M, *et al*. PD-L1 is an independent prognostic predictor in gastric cancer of western patients. Oncotarget, 2016, **7**(17): 24269-24283

[8] Jiang Y, Chen M, Nie H, *et al*. PD-1 and PD-L1 in cancer immunotherapy: clinical implications and future considerations. Hum Vaccin Immunother, 2019, **15**(5): 1111-1122

[9] Gibbons Johnson R M, Dong H. Functional expression of programmed death-Ligand 1 (B7-H1) by immune cells and tumor cells. Front Immunol, 2017, **8**: 961

[10] Dong W, Wu X, Ma S, *et al*. The mechanism of anti-PD-L1 antibody efficacy against PD-L1-negative tumors identifies NK cells expressing PD-L1 as a cytolytic effector. Cancer Discov, 2019, **9**(10): 1422-1437

[11] Shen X, Zhang L, Li J, *et al*. Recent findings in the regulation of programmed death ligand 1 expression. Front Immunol, 2019, **10**: 1337

[12] Thakur N, Paik K Y, Hwang G, *et al*. High expression of PD-L1 is associated with better survival in pancreatic/periampullary cancers and correlates with epithelial to mesenchymal transition. Diagnostics (Basel), 2021, **11**(4): 597

[13] Zhang K, Kong X, Li Y, *et al*. PD-1/PD-L1 inhibitors in patients with preexisting autoimmune diseases. Front Pharmacol, 2022, **13**: 854967

[14] Schönrich G, Raftery M J. The PD-1/PD-L1 axis and virus infections: a delicate balance. Front Cell Infect Microbiol, 2019, **9**: 207

[15] Kaiho T, Suzuki H, Hata A, *et al*. Targeting PD-1/PD-L1 inhibits rejection in a heterotopic tracheal allograft model of lung transplantation. Front Pharmacol, 2023, **14**: 1298085

[16] Li Q, Han J, Yang Y, *et al*. PD-1/PD-L1 checkpoint inhibitors in advanced hepatocellular carcinoma immunotherapy. Front Immunol, 2022, **13**: 1070961

[17] Bevins N J, Okamura R, Montesion M, *et al*. Tumor infiltrating lymphocyte expression of PD-1 predicts response to anti-PD-1/PD-L1 immunotherapy. J Immunother Precis Oncol, 2022, **5**(4): 90-97

[18] Oestreich K J, Yoon H, Ahmed R, *et al*. NFATc1 regulates PD-1 expression upon T cell activation. J Immunol, 2008, **181**(7): 4832-4839

[19] Shaulian E, Karin M. AP-1 as a regulator of cell life and death. Nat

Cell Biol, 2002, **4**(5): E131-E136

[20] Xiao G, Deng A, Liu H, *et al*. Activator protein 1 suppresses antitumor T-cell function *via* the induction of programmed death 1. Proc Natl Acad Sci USA, 2012, **109**(38): 15419-15424

[21] Kao C, Oestreich K J, Paley M A, *et al*. Transcription factor T-bet represses expression of the inhibitory receptor PD-1 and sustains virus-specific CD8+ T cell responses during chronic infection. Nat Immunol, 2011, **12**(7): 663-671

[22] Yu X, Gao R, Li Y, *et al*. Regulation of PD-1 in T cells for cancer immunotherapy. Eur J Pharmacol, 2020, **881**: 173240

[23] Bally A P, Lu P, Tang Y, *et al*. NF-κB regulates PD-1 expression in macrophages. J Immunol, 2015, **194**(9): 4545-4554

[24] Lim T S, Chew V, Sieow J L, *et al*. PD-1 expression on dendritic cells suppresses CD8(+) T cell function and antitumor immunity. Oncoimmunology, 2016, **5**(3): e1085146

[25] Luo C, Hajkova P, Ecker J R. Dynamic DNA methylation: in the right place at the right time. Science, 2018, **361**(6409): 1336-1340

[26] Youngblood B, Oestreich K J, Ha S J, *et al*. Chronic virus infection enforces demethylation of the locus that encodes PD-1 in antigen-specific CD8(+) T cells. Immunity, 2011, **35**(3): 400-412

[27] Wei H, Xie A, Li J, *et al*. PD-1(+) CD4 T cell immune response is mediated by HIF-1α/NFATc1 pathway after *P. yoelii* infection. Front Immunol, 2022, **13**: 942862

[28] Bally A P R, Neeld D K, Lu P, *et al*. PD-1 expression during acute infection is repressed through an LSD1-Blimp-1 axis. J Immunol, 2020, **204**(2): 449-458

[29] Mclane L M, Ngiow S F, Chen Z, *et al*. Role of nuclear localization in the regulation and function of T-bet and Eomes in exhausted CD8 T cells. Cell Rep, 2021, **35**(6): 109120

[30] Austin J W, Lu P, Majumder P, *et al*. STAT3, STAT4, NFATc1, and CTCF regulate PD-1 through multiple novel regulatory regions in murine T cells. J Immunol, 2014, **192**(10): 4876-4886

[31] Wei T, Wang K, Liu S, *et al*. Periostin deficiency reduces PD-1(+) tumor-associated macrophage infiltration and enhances anti-PD-1 efficacy in colorectal cancer. Cell Rep, 2023, **42**(2): 112090

[32] Tanaka A, Zhou Y, Ogawa M, *et al*. STAT1 as a potential prognosis marker for poor outcomes of early stage colorectal cancer with microsatellite instability. PLoS One, 2020, **15**(4): e0229252

[33] Mathieu M, Cotta-Grand N, Daudelin J F, *et al*. Notch signaling regulates PD-1 expression during CD8(+) T-cell activation. Immunol Cell Biol, 2013, **91**(1): 82-88

[34] Hemmatzadeh M, Ahangar Parvin E, Ghanavatinejad A, *et al*. MicroRNAs targeting programmed cell death protein 1 (PD-1) promote natural killer cell exhaustion in rheumatoid arthritis. Iran J Allergy Asthma Immunol, 2022, **21**(6): 646-656

[35] Lv J, Qin L, Zhao R, *et al*. Disruption of CISH promotes the antitumor activity of human T cells and decreases PD-1 expression levels. Mol Ther Oncolytics, 2023, **28**: 46-58

[36] Nüssing S, Koay H F, Sant S, *et al*. Divergent SATB1 expression across human life span and tissue compartments. Immunol Cell Biol, 2019, **97**(5): 498-511

[37] Ren L, Li Z, Zhou Y, *et al*. CBX4 promotes antitumor immunity by suppressing Pdcd1 expression in T cells. Mol Oncol, 2023, **17**(12): 2694-2708

[38] Garcia-Diaz A, Shin D S, Moreno B H, *et al*. Interferon receptor signaling pathways regulating PD-L1 and PD-L2 expression. Cell Rep, 2017, **19**(6): 1189-1201

[39] Concha-Benavente F, Srivastava R M, Trivedi S, *et al*. Identification of the cell-intrinsic and -extrinsic pathways downstream of EGFR and IFNγ that induce PD-L1 expression in head and neck cancer. Cancer Res, 2016, **76**(5): 1031-1043

[40] Wu B, Song M, Dong Q, *et al*. UBR5 promotes tumor immune evasion through enhancing IFN-γ-induced *PDL1* transcription in triple negative breast cancer. Theranostics, 2022, **12**(11): 5086-5102

[41] Green M R, Monti S, Rodig S J, *et al*. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction *via* JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood, 2010, **116**(17): 3268-3277

[42] Roemer M G, Advani R H, Ligon A H, *et al*. PD-L1 and PD-L2 genetic alterations define classical hodgkin lymphoma and predict outcome. J Clin Oncol, 2016, **34**(23): 2690-2697

[43] George J, Saito M, Tsuta K, *et al*. Genomic amplification of CD274 (PD-L1) in small-cell lung cancer. Clin Cancer Res, 2017, **23**(5): 1220-1226

[44] Antonangeli F, Natalini A, Garassino M C, *et al*. Regulation of PD-L1 expression by NF-κB in cancer. Front Immunol, 2020, **11**: 584626

[45] Ding X C, Wang L L, Zhang X D, *et al*. The relationship between expression of PD-L1 and HIF-1α in glioma cells under hypoxia. J Hematol Oncol, 2021, **14**(1): 92

[46] Yan Y, Zheng L, Du Q, *et al*. Interferon regulatory factor 1 (IRF-1) and IRF-2 regulate PD-L1 expression in hepatocellular carcinoma (HCC) cells. Cancer Immunol Immunother, 2020, **69**(9): 1891-1903

[47] Mittendorf E A, Philips A V, Meric-Bernstam F, *et al*. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res, 2014, **2**(4): 361-370

[48] Shen X, Jin X, Fang S, *et al*. EFEMP2 upregulates PD-L1 expression *via* EGFR/ERK1/2/c-Jun signaling to promote the invasion of ovarian cancer cells. Cell Mol Biol Lett, 2023, **28**(1): 53

[49] Yang H, Xue M, Su P, *et al*. RNF31 represses cell progression and immune evasion *via* YAP/PD-L1 suppression in triple negative breast Cancer. J Exp Clin Cancer Res, 2022, **41**(1): 364

[50] Casey S C, Tong L, Li Y, *et al*. MYC regulates the antitumor immune response through CD47 and PD-L1. Science, 2016, **352**(6282): 227-231

[51] Long S, Huang G, Ouyang M, *et al*. Epigenetically modified AP-2α by DNA methyltransferase facilitates glioma immune evasion by upregulating PD-L1 expression. Cell Death Dis, 2023, **14**(6): 365

[52] Vaxevanis C K, Friedrich M, Tretbar S U, *et al*. Identification and

characterization of novel CD274 (PD-L1) regulating microRNAs and their functional relevance in melanoma. Clin Transl Med, 2022, **12**(7): e934

[53] Luo C, Xin H, Zhou Z, *et al*. Tumor-derived exosomes induce immunosuppressive macrophages to foster intrahepatic cholangiocarcinoma progression. Hepatology, 2022, **76**(4): 982-999

[54] Shen C, Zhang Z, Tian Y, *et al*. Sulforaphane enhances the antitumor response of chimeric antigen receptor T cells by regulating PD-1/PD-L1 pathway. BMC Med, 2021, **19**(1): 283

[55] Zhang T, Yu H, Dai X, *et al*. CMTM6 and CMTM4 as two novel regulators of PD-L1 modulate the tumor microenvironment. Front Immunol, 2022, **13**: 971428

[56] Liu C, Yao Z, Wang J, *et al*. Macrophage-derived CCL5 facilitates immune escape of colorectal cancer cells *via* the p65/STAT3-CSN5-PD-L1 pathway. Cell Death Differ, 2020, **27**(6): 1765-1781

[57] Chen X, Wang K, Jiang S, *et al*. eEF2K promotes PD-L1 stabilization through inactivating GSK3β in melanoma. J Immunother Cancer, 2022, **10**(3): e004026

[58] Chan L C, Li C W, Xia W, *et al*. IL-6/JAK1 pathway drives PD-L1 Y112 phosphorylation to promote cancer immune evasion. J Clin Invest, 2019, **129**(8): 3324-3338

[59] Čaval T, Alisson-Silva F, Schwarz F. Roles of glycosylation at the cancer cell surface: opportunities for large scale glycoproteomics. Theranostics, 2023, **13**(8): 2605-2615

[60] Wang S, Iyer R, Han X, *et al*. CRISPR screening identifies the deubiquitylase ATXN3 as a PD-L1-positive regulator for tumor immune evasion. J Clin Invest, 2023, **133**(23): e167728

[61] Lu C, Paschall A V, Shi H, *et al*. The MLL1-H3K4me3 axis-mediated PD-L1 expression and pancreatic cancer immune evasion. J Natl Cancer Inst, 2017, **109**(6): djw283

[62] Larsen T V, Dybdal N, Daugaard T F, *et al*. Examination of the functional relationship between PD-L1 DNA methylation and mRNA expression in non-small-cell lung cancer. Cancers (Basel), 2023, **15**(6): 1909

[63] Adeshakin A O, Adeshakin F O, Yan D, *et al*. Regulating histone deacetylase signaling pathways of myeloid-derived suppressor cells enhanced T cell-based immunotherapy. Front Immunol, 2022, **13**: 781660

[64] Ramos-Casals M, Brahmer J R, Callahan M K, *et al*. Immune-related adverse events of checkpoint inhibitors. Nat Rev Dis Primers, 2020, **6**(1): 38

[65] Francisco L M, Sage P T, Sharpe A H. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev, 2010, **236**: 219-242

[66] Teng F, Meng X, Kong L, *et al*. Progress and challenges of predictive biomarkers of anti PD-1/PD-L1 immunotherapy: a systematic review. Cancer Lett, 2018, **414**: 166-173

[67] Kim W, Chu T H, Nienhüser H, *et al*. PD-1 signaling promotes tumor-infiltrating myeloid-derived suppressor cells and gastric tumorigenesis in mice. Gastroenterology, 2021, **160**(3): 781-796

[68] Martins C, Rasbach E, Heppt M V, *et al*. Tumor cell-intrinsic PD-1 promotes Merkel cell carcinoma growth by activating downstream mTOR-mitochondrial ROS signaling. Sci Adv, 2024, **10**(3): eadi2012

[69] Gyukity-Sebestyén E, Harmati M, Dobra G, *et al*. Melanoma-derived exosomes induce PD-1 overexpression and tumor progression *via* mesenchymal stem cell oncogenic reprogramming. Front Immunol, 2019, **10**: 2459

[70] Li H, Li X, Liu S, *et al*. Programmed cell death-1 (PD-1) checkpoint blockade in combination with a mammalian target of rapamycin inhibitor restrains hepatocellular carcinoma growth induced by hepatoma cell-intrinsic PD-1. Hepatology, 2017, **66**(6): 1920-1933

[71] Barden M M, Omuro A M. Top advances of the year: Neuro-oncology. Cancer, 2023, **129**(10): 1467-1472

[72] Pu N, Gao S, Yin H, *et al*. Cell-intrinsic PD-1 promotes proliferation in pancreatic cancer by targeting CYR61/CTGF *via* the hippo pathway. Cancer Lett, 2019, **460**: 42-53

[73] Wang X, Yang X, Zhang C, *et al*. Tumor cell-intrinsic PD-1 receptor is a tumor suppressor and mediates resistance to PD-1 blockade therapy. Proc Natl Acad Sci USA, 2020, **117**(12): 6640-6650

[74] Qu J, Chen Q, Bing Z, *et al*. *C. tropicalis* promotes CRC by down-regulating tumor cell-intrinsic PD-1 receptor *via* autophagy. J Cancer, 2023, **14**(10): 1794-1808

[75] Kong X, Peng H, Liu P, *et al*. Programmed death ligand 1 regulates epithelial-mesenchymal transition and cancer stem cell phenotypes in hepatocellular carcinoma through the serum and glucocorticoid kinase 2/β-catenin signaling pathway. Cancer Sci, 2023, **114**(6): 2265-2276

[76] Ma Y, Marinkova R, Nenkov M, *et al*. Tumor-intrinsic PD-L1 exerts an oncogenic function through the activation of the Wnt/β-Catenin pathway in human non-small cell lung cancer. Int J Mol Sci, 2022, **23**(19): 11031

[77] Jha A, Alam M, Kashyap T, *et al*. Crosstalk between PD-L1 and Jak2-Stat3/MAPK-AP1 signaling promotes oral cancer progression, invasion and therapy resistance. Int Immunopharmacol, 2023, **124**(Pt A): 110894

[78] Chen C, Li S, Xue J, *et al*. PD-L1 tumor-intrinsic signaling and its therapeutic implication in triple-negative breast cancer. JCI Insight, 2021, **6**(8): e131458

[79] Sung H, Ferlay J, Siegel R L, *et al*. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, 2021, **71**(3): 209-249

[80] Wang D K, Zuo Q, He Q Y, *et al*. Targeted immunotherapies in gastrointestinal cancer: from molecular mechanisms to implications. Front Immunol, 2021, **12**: 705999

[81] Zeng Y, Jin R U. Molecular pathogenesis, targeted therapies, and future perspectives for gastric cancer. Semin Cancer Biol, 2022, **86**(Pt 3): 566-582

[82] Zhang S X, Liu W, Ai B, *et al*. Current advances and outlook in gastric cancer chemoresistance: a review. Recent Pat Anticancer Drug Discov, 2022, **17**(1): 26-41

[83] Li G Z, Doherty G M, Wang J. Surgical management of gastric

cancer: a review. JAMA Surg, 2022, **157**(5): 446-454

[84] Nohria A, Kaslow S R, Hani L, *et al*. Outcomes after surgical palliation of patients with gastric cancer. J Surg Res, 2022, **279**: 304-311

[85] Li K, Zhang A, Li X, *et al*. Advances in clinical immunotherapy for gastric cancer. Biochim Biophys Acta Rev Cancer, 2021, **1876**(2): 188615

[86] Smyth E, Knödler M, Giraut A, *et al*. Vestige: adjuvant immunotherapy in patients with resected esophageal, gastroesophageal junction and gastric cancer following preoperative chemotherapy with high risk for recurrence (N+ and/or R1): an open label randomized controlled phase-2-study. Front Oncol, 2019, **9**: 1320

[87] Bang Y J, Van Cutsem E, Fuchs C S, *et al*. KEYNOTE-585: phase III study of perioperative chemotherapy with or without pembrolizumab for gastric cancer. Future Oncol, 2019, **15**(9): 943-952

[88] Janjigian Y Y, Shitara K, Moehler M, *et al*. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. Lancet, 2021, **398**(10294): 27-40

[89] Sun J M, Shen L, Shah M A, *et al*. Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study. Lancet, 2021, **398**(10302): 759-771

[90] Kang Y K, Boku N, Satoh T, *et al*. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet, 2017, **390**(10111): 2461-2471

[91] Fuchs C S, Doi T, Jang R W, *et al*. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol, 2018, **4**(5): e180013

[92] Xu J, Jiang H, Pan Y, *et al*. LBA53 Sintilimab plus chemotherapy (chemo) versus chemo as first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16): first results of a randomized, double-blind, phase III study. Ann Oncol, 2021, **32**: 1331

[93] Xu R H, Arkenau H T, Bang Y J, *et al*. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line therapy in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma. J Clin Oncol, 2020, **38**(4): 458

[94] Catenacci D V, Rosales M, Chung H C, *et al*. MAHOGANY: margetuximab combination in HER2+ unresectable/metastatic gastric/gastroesophageal junction adenocarcinoma. Future Oncol, 2021, **17**(10): 1155-1164

[95] Catenacci D V T, Rosales M K, Chung H C, *et al*. Margetuximab (M) combined with anti-PD-1 (retifanlimab) or anti-PD-1/LAG-3 (tebotelimab) +/- chemotherapy (CTX) in first-line therapy of advanced/metastatic HER2+ gastroesophageal junction (GEJ) or gastric cancer (GC). J Clin Oncol, 2021, **39**(3): TPS264-TPS264

[96] Al-Batran S E, Lorenzen S, Thuss-Patience P C, *et al*. 1494P updated safety data of the DANTE trial: perioperative atezolizumab in combination with FLOT versus FLOT alone in patients with resectable esophagogastric adenocarcinoma - a randomized, open-label phase II trial of the German Gastric Group at the AIO and SAKK. Ann Oncol, 2020, **31**: S927-S928

[97] Högner A, Breithaupt K, Stein A, *et al*. RAP: a phase II trial with ramucirumab, avelumab, and paclitaxel as second line treatment in gastro-esophageal adenocarcinoma of the arbeitsgemeinschaft internistische onkologie (AIO). J Clin Oncol, 2019, **37**(15): TPS4148-TPS4148

[98] Bang Y J, Ruiz E Y, Van Cutsem E, *et al*. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol, 2018, **29**(10): 2052-2060

[99] Janjigian Y Y, Cutsem E V, Muro K, *et al*. MATTERHORN: efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy in resectable gastric and gastroesophageal junction cancer—a randomized, double-blind, placebo-controlled, phase 3 study. J Clin Oncol, 2021, **39**(15): TPS4151-TPS4151

[100] Palle J, Rochand A, Pernot S, *et al*. Human epidermal growth factor receptor 2 (HER2) in advanced gastric cancer: current knowledge and future perspectives. Drugs, 2020, **80**(4): 401-415

[101] Shitara K, Baba E, Fujitani K, *et al*. Discovery and development of trastuzumab deruxtecan and safety management for patients with HER2-positive gastric cancer. Gastric Cancer, 2021, **24**(4): 780-789

[102] Janjigian Y Y, Kawazoe A, Yanez P E, *et al*. Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: initial findings of the global phase 3 KEYNOTE-811 study. J Clin Oncol, 2021, **39**(15): 4013

[103] Biller L H, Schrag D. Diagnosis and treatment of metastatic colorectal cancer: a review. JAMA, 2021, **325**(7): 669-685

[104] Arnold M, Sierra M S, Laversanne M, *et al*. Global patterns and trends in colorectal cancer incidence and mortality. Gut, 2017, **66**(4): 683-691

[105] Turk S, Plahuta I, Magdalenic T, *et al*. Two-stage hepatectomy in resection of colorectal liver metastases - a single-institution experience with case-control matching and review of the literature. Radiol Oncol, 2023, **57**(2): 270-278

[106] Bhattacharyya N P, Skandalis A, Ganesh A, *et al*. Mutator phenotypes in human colorectal carcinoma cell lines. Proc Natl Acad Sci USA, 1994, **91**(14): 6319-6323

[107] Overman M J, Ernstoff M S, Morse M A. Where we stand with immunotherapy in colorectal cancer: deficient mismatch repair,

proficient mismatch repair, and toxicity management. Am Soc Clin Oncol Educ Book, 2018, **38**: 239-247

[108] Pawlik T M, Raut C P, Rodriguez-Bigas M A. Colorectal carcinogenesis: MSI-H versus MSI-L. Dis Markers, 2004, **20**(4-5): 199-206

[109] Salipante S J, Scroggins S M, Hampel H L, *et al*. Microsatellite instability detection by next generation sequencing. Clin Chem, 2014, **60**(9): 1192-1199

[110] Boland C R, Thibodeau S N, Hamilton S R, *et al*. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res, 1998, **58**(22): 5248-5257

[111] Zaanan A, Shi Q, Taieb J, *et al*. Role of deficient DNA mismatch repair status in patients with stage III colon cancer treated with FOLFOX adjuvant chemotherapy: a pooled analysis from 2 randomized clinical trials. JAMA Oncol, 2018, **4**(3): 379-383

[112] Romero D. New first-line therapy for dMMR/MSI-H CRC. Nat Rev Clin Oncol, 2021, **18**(2): 63

[113] Venderbosch S, Nagtegaal I D, Maughan T S, *et al*. Mismatch repair status and BRAF mutation status in metastatic colorectal cancer patients: a pooled analysis of the CAIRO, CAIRO2, COIN, and FOCUS studies. Clin Cancer Res, 2014, **20**(20): 5322-5330

[114] Wrobel P, Ahmed S. Current status of immunotherapy in metastatic colorectal cancer. Int J Colorectal Dis, 2019, **34**(1): 13-25

[115] Samstein R M, Lee C H, Shoushtari A N, *et al*. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet, 2019, **51**(2): 202-206

[116] Chan T A, Yarchoan M, Jaffee E, *et al*. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Ann Oncol, 2019, **30**(1): 44-56

[117] Mukherji R, Weinberg B A, Pedersen K S. Immunotherapy for colorectal cancer. Hematol Oncol Clin North Am, 2022, **36**(3): 603-626

[118] Yarchoan M, Johnson B A 3rd, Lutz E R, *et al*. Targeting neoantigens to augment antitumour immunity. Nat Rev Cancer, 2017, **17**(4): 209-222

[119] Le D T, Durham J N, Smith K N, *et al*. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science, 2017, **357**(6349): 409-413

[120] André T, Shiu K K, Kim T W, *et al*. Pembrolizumab in microsatellite-instability-high advanced colorectal cancer. N Engl J Med, 2020, **383**(23): 2207-2218

[121] Zhang C, Li D, Xiao B, *et al*. B2M and JAK1/2-mutated MSI-H colorectal carcinomas can benefit from anti-PD-1 therapy. J Immunother, 2022, **45**(4): 187-193

[122] Le D T, Uram J N, Wang H, *et al*. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med, 2015, **372**(26): 2509-2520

[123] Overman M J, Mcdermott R, Leach J L, *et al*. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. Lancet Oncol, 2017, **18**(9): 1182-1191

[124] Overman M J, Lonardi S, Wong K Y M, *et al*. Durable clinical benefit with nivolumab plus ipilimumab in DNA mismatch repair-deficient/microsatellite instability-high metastatic colorectal cancer. J Clin Oncol, 2018, **36**(8): 773-779

[125] Hochster H S, Bendell J C, Cleary J M, *et al*. Efficacy and safety of atezolizumab (atezo) and bevacizumab (bev) in a phase Ib study of microsatellite instability (MSI)-high metastatic colorectal cancer (mCRC). J Clin Oncol, 2017, **35**(4): 673

[126] Lakins M A, Koers A, Giambalvo R, *et al*. FS222, a CD137/PD-L1 tetravalent bispecific antibody, exhibits low toxicity and antitumor activity in colorectal cancer models. Clin Cancer Res, 2020, **26**(15): 4154-4167

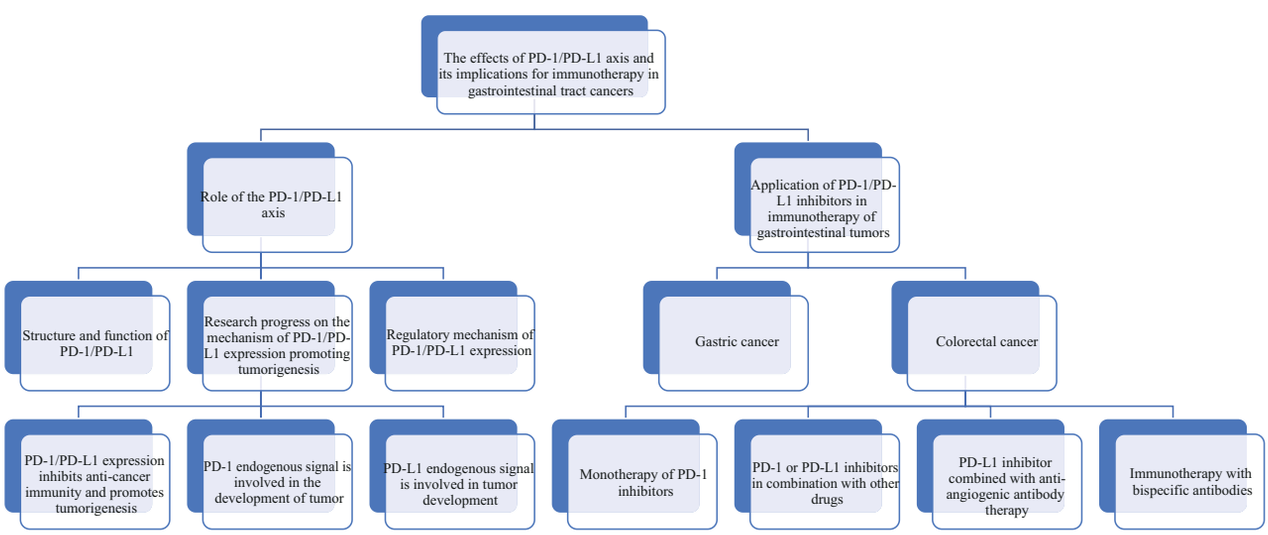
The Effects of The PD−1/PD−L1 Axis and Its Implications for Immunotherapy in Gastrointestinal Tract Cancers*

CAO Xin[1,2], ZHANG Jin-Ping[2], TU Li-Ying[1,2], ZOU Yun-Lian[2]**

([1]*Medical School, Kunming University of Science and Technology, Kunming* 650500, China;

[2]*Department of Hematology, The First People's Hospital of Yunnan Province, Kunming* 650100, China)

Graphical abstract



Abstract Programmed death-1 (PD-1) is an inhibitory immune checkpoint that binds to programmed death-ligand 1 (PD-L1) to regulate the immune response and maintain immune system homeostasis of the immune system. Through overexpression of PD-L1, tumor cells bind to PD-1 on the surface of immune cells, inhibiting the activity and function of immune cells, leading to immune escape of cancer cells and tumor progression. Gastrointestinal cancer is a common malignancy with a high mortality rate worldwide, and the effectiveness of current systematic treatment options is limited. In recent years, immune checkpoint inhibitors (ICIs) such as PD-1/PD-L1 inhibitors have attracted much attention in cancer therapy. Immunotherapy has been incorporated into the treatment of some gastrointestinal malignancies. Different from traditional treatment, it uses various means to stimulate and enhance the immune function of the body to achieve the therapeutic purpose of controlling and eliminating tumor cells. However, although PD-1/PD-L1 inhibitors have shown potential in the treatment of gastrointestinal tumors, the efficacy of single inhibitor therapy is limited, which may be due to the ability of

* This work was supported by grants from Science and Technology Plan Project of Science and Technology Department of Yunnan Province (202101AY070001-027) and Yunnan Clinical Medical Center Open Project (2020LCZXKF-XY08).

** Corresponding author.

Tel：86-13708893386，E-mail：zouyunlian825046@sina.com

Received：November 6，2023 Accepted：March 4，2024

tumors to escape immune attack through other pathways after inhibitor treatment, or the presence of other immunosuppressive factors. For example, PD-1 and PD-L1 inhibitors can be combined with other immune checkpoint drugs, molecularly targeted drugs, or chemotherapy drugs to simultaneously act on different immune pathways and improve the comprehensive effect of immunotherapy. However, to achieve an effective combination therapy, we need to delve into the specific mechanisms of action of the PD-1/PD-L1 axis in the development and progression of gastrointestinal tumors, which can help to develop the best treatment strategy and provide individualized treatment options for the appropriate patient population. Therefore, future studies should focus on the regulatory mechanisms of PD-1/PD-L1 axis and evaluate the therapeutic effects of different treatment combinations on gastrointestinal tumors. In this paper, we review the research progress of PD-1/PD-L1 axis in tumorigenicity and its mechanism, and review the single and combined treatment strategies of PD-1 and PD-L1 inhibitors in gastrointestinal tumors.

Key words PD-1, PD-L1, gastrointestinal tumors, immunotherapy
DOI：10.16476/j.pibb.2023.0434